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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,527	KOO ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,29-39,41-44 and 47-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,29-39,41-44 and 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 12, 2007 has been entered. Claims 1-27, 29-39, 41-44, and 47-50 are currently pending and will be examined.

Information Disclosure Statement

2. The Information Disclosure Statement filed January 23, 2007 has been considered. A signed copy is attached herewith.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47 and 48 recite the limitation "the double-stranded molecule" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-7, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1; cited previously) in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited).

Regarding claim 1, Kneipp teaches a method comprising:

(a) separating a DNA or RNA fragment comprising a purine or pyrimidine base from the nucleic acid molecule (paragraphs 62-63 and claim 20, where Kneipp teaches that fragments may be at least a nucleotide; see also paragraph 43, where Kneipp teaches that the fragment may be a nucleotide or a nucleoside)

(b) depositing the separated base-containing fragment on a SERS substrate (paragraphs 63 & 48)

(c) detecting the separated base-containing fragment using SERS (paragraphs 63 & 57).

Regarding claim 2, Kneipp teaches detection of a dNTP (see paragraph 43 and also claim 20).

Regarding claim 3, Kneipp teaches fragmenting the DNA or RNA sample with an exonuclease (paragraphs 63-64). This mixture of DNA or RNA and exonuclease is a sequencing mixture.

Regarding claim 4, Kneipp teaches labeling with a Raman label prior to SERS detection (paragraph 42).

Regarding claims 5-7, Kneipp teaches detection of nucleotides comprising the purine bases adenine and guanine (see claim 19, page 10).

Regarding claim 13, Kneipp teaches that the separated base-containing fragments are deposited on silver nanoparticles (see paragraphs 63 and 47-50, where Kneipp teaches depositing cleaved fragments on nanoscale aggregates of silver nanoparticles).

Kneipp does not teach removing the deoxyribose or ribose moiety from the cleaved base-containing fragment. Kneipp also does not teach contacting the separated base with an alkali-metal halide salt.

Otto measured surfaced enhanced raman (SERS) spectra for adenine, 2'-deoxyadenosine, dAMP, poly(rA), and denatured DNA (see abstract).

Regarding claim 1, Otto teaches that the although the SERS spectra for the free nucleotide bases (adenine, guanine, thymine, cytosine, and uracil) are very intense, similarly intense signals were not observed with denatured DNA molecules (see page 1240). Otto then determined that reproducible SERS spectra also could not be obtained for the free nucleotides (dGMP, dUMP, dTMP, dCMP) with the exception of dAMP (page 1240, col. 2). Otto concluded that this inability to obtain reproducible SERS spectra was the result of interference from the sugar-phosphate moiety and stated, "These observations led us to believe that only in the case of dAMP the adsorption is not hampered by the sugar-phosphate group. That is, the presence of the sugar-phosphate group at the N1-position of cytosine, thymine, or uracil and at the N9-position of guanine prevents the adsorption of these nucleotides to the silver surface (page 1240, column 2 – page 1241, column 1)."

Regarding claim 14, Otto teaches adsorption of the base-containing fragments in a solution of the alkali-metal halide salts KCl or KI (page 1240, column 2). Otto teaches that the these solutions further enhance the observed signal (page 1240, column 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to separate the sugar-phosphate moiety from the cleaved purine or pyrimidine base-containing fragment in the method taught by Kneipp. As discussed above, Otto taught that the presence of the sugar-phosphate group prevented adsorption of dTMP, dUMP, dCMP, and dGMP to a SERS substrate (pages 1240-1241). An ordinary practitioner of the method taught by Kneipp would have been motivated by these teachings of Otto to remove the sugar-phosphate moiety from the cleaved base-containing fragment prior to deposition on the SERS substrate in order to improve the adsorption ability of the base. Since enzymes capable of removing the

sugar-phosphate group were known in the art and commercially available at the time of invention, an ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Otto to the sequencing method taught by Kneipp. Also, an ordinary practitioner would have been motivated by the teachings of Otto to deposit the cleaved base on the SERS substrate in the presence of an alkali-metal halide salt such as KCl or KI, since Otto taught that these solutions enhanced the observed SERS signal. Therefore, an ordinary practitioner of the SERS-based nucleic acid sequencing method taught by Kneipp, interested in improving adsorption of cleaved bases to the SERS substrate and enhancing the observed signal, would have been motivated to additionally remove the sugar-phosphate group prior to adsorption and conduct the adsorption step in the presence of an alkali-metal halide salt as suggested by Otto, thus resulting in the instantly claimed methods.

6. Claims 8-12 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1; cited previously) as evidenced by Ulmer et al. (US 5,674,743; newly cited) in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Liang et al. (Chemical Physics Letters (1994) 227: 115-120; cited previously).

The combined teachings of Kneipp and Otto result in the method of claims 1-7, 13 and 14, as discussed above.

Regarding claim 8, Kneipp teaches the use of SERS for detection, but not SECARS.

Regarding claims 9-12, Kneipp teaches detection of pyrimidine bases including thymine, cytosine, and uracil (see claim 19, page 10).

Regarding claim 16, Kneipp teaches a method comprising:

(a) obtaining a target molecule (paragraph 63)

(b) separating a DNA or RNA fragment comprising a purine or pyrimidine base from the nucleic acid molecule (paragraphs 62-63 and claim 20, where Kneipp teaches that fragments may be at least a nucleotide; see also paragraph 43, where Kneipp teaches that the fragment may be a nucleotide or a nucleoside)

(c) depositing the separated base-containing fragment on a SERS substrate (paragraphs 63 & 48)

(d) detecting the separated base-containing fragment using SERS (paragraphs 63 & 57).

Further regarding claim 16, Kneipp teaches SERS detection rather than SECARS.

Regarding claim 17, Kneipp does not specifically teach isolation of DNA or RNA from biological materials. However, Kneipp cites the teachings of Ulmer et al. (US 5,674,743) at paragraph 10. Ulmer teaches sequencing of DNA from biological sources at column 17, lines 34-48, thereby demonstrating the Kneipp contemplated applying the SERS sequencing method to DNA isolated from biological sources.

Regarding claims 18-23, Kneipp teaches detection of dNTPs and also pyrimidine bases including thymine, cytidine and uracil (see claims 19-20, page 10).

As noted above, Kneipp teaches SERS detection rather than SECARS detection.

Liang reports the experimental observation of SECARS (abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute SECARS detection for SERS detection in the method resulting from the

combined teachings of Kneipp and Otto. Liang taught that surface enhancement (SECARS) produced a Raman signal significantly enhanced relative to CARS with improved signal-to-noise (abstract). Since the CARS method, which results from excitation with dual lasers, was known to produce a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique as suggested by Liang in order to improve the sensitivity of the detection method of Kneipp. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS detection for SERS detection in the method of Kneipp. Therefore, the ordinary practitioner of the SERS sequencing method resulting from the combined teachings of Kneipp and Otto, interested in obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

7. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1; cited previously) in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Chen et al. (Chemical Physics Letters (1984) 108(1): 32-38; newly cited).

The combined teachings of Kneipp and Otto result in the method of claim 14, as discussed above.

Neither Kneipp nor Otto teaches that the alkali-metal halide salt is lithium chloride.

Chen teaches alkali-metal halide salt solutions including NaCl, LiCl, HCl, $MgCl_2$, NaBr, CsI, RbI, LiI, KCN, and NaN_3 are SERS-active solutions (page 32, col. 1 and also the abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute LiCl for KCl or KI in the method resulting from the combined teachings of Kneipp and Otto. An ordinary practitioner would have been motivated by the teachings of Chen to use any known SERS-active solution, such as LiCl, in order to enhance the observed Raman signal. Since Chen taught that several alkali-metal halide salt solutions (including LiCl and $MgCl_2$) were SERS-active, the ordinary user would have been motivated to utilize any one of these art-recognized equivalents for SERS signal enhancement. As noted in MPEP 2144.06, it is prima facie obvious to substitute art-recognized equivalents for the same purpose. Therefore, the method of the instant claim 15 is prima facie obvious in view of the combined teachings of Kneipp, Otto, and Chen.

8. Claims 24-27, 30-37, 39, 41-44, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melamede (US 4,863,849; cited previously) in view of Vo-Dinh (US 5,306,403; cited previously) and further in view of Otto et al. (Journal of Chemical Physics (1988) 92: 1239-1244; newly cited).

Melamede teaches a primer extension-based method of nucleic acid sequencing (see Figures 1-3 and column 11, line 20 – column 14, line 27 for a general description).

Regarding claims 24 and 34, the method of Melamede comprises:

(a) contacting a detectable and known number of single-stranded template nucleic acid molecules with a mixture comprising a primer, a polymerase, and a known initial concentration

of a first nucleotide, where the primer or single-stranded target is immobilized on a surface of the reaction chamber (column 6, lines 39-44 teach adding the reaction mixture to the single-stranded template; column 12, line 58 – column 13, line 3 teach that the initial concentration of the first dNTP is known; column 12, lines 26-30 teach immobilization of the primed template; column 15, lines 55-58 teach using a known and detectable concentration of template; see also Figures 2 & 3 for a schematic of the method)

(b) annealing the primer to the single-stranded template nucleic acid (column 6, lines 39-44; see also column 12, lines 26-33)

(c) synthesizing a double-stranded molecule comprising the first nucleotide and the single-stranded template (column 6, lines 39-49; see also column 12, line 58 – column 13, line 3)

(d) depositing the post-reaction mixture on a substrate (column 12, lines 39-45), or alternately, flowing the post-reaction mixture past a detector (column 11, line 66 – column 12, line 16; see also column 12, line 58 – column 13, line 3)

(e) detecting a concentration of the first nucleotide using absorption or fluorescence spectroscopy, radioactive labeling, or electrochemical detection (see column 6, lines 48-66 and column 14, lines 15-29), thereby determining whether or not the nucleotide was incorporated into the nascent polynucleotide strand.

Regarding claims 25 and 26, Melamede teaches that the concentration of the first nucleotide is greater than the concentration of the single-stranded template, and specifically teaches using a first dNTP concentration four times greater than the single-stranded template concentration (column 12, line 58 – column 13, line 3).

Regarding claim 27, Melamede teaches adding additional first nucleotide to the reaction mixture after detecting the concentration of the first nucleotide (column 13, lines 19-25; see also column 15, lines 55-64).

Regarding claims 30 and 35, Melamede teaches repeating the process of claim 24 using a different nucleotide (column 15, line 55 – column 16, line 2, where dGTP is the first nucleotide and dCTP is the 2nd nucleotide; see also Figure 2).

Regarding claims 32, 33, 43, and 44, Melamede teaches inclusion of an internal control and comparing the intensity observed from the internal control to that observed from the first nucleotide in order to determine which nucleotide has been incorporated into the template (see column 10, lines 7-10, where inclusion of multiple, different dNTPs is taught; the dNTPs not expected to be incorporated (col. 10, lines 9-10 teach that the template sequence is known) are internal controls).

Regarding claim 36, Melamede teaches washing the substrate (column 6, lines 48-54).

Regarding claim 37, Melamede teaches that the reaction time is about 1 second to about 10 minutes (see column 16, lines 23-38, where the SEQ program is cited; the program has a default reaction time of 1.5 (see line 420 in column 17/18)). Either 1.5 seconds or 1.5 minutes for the reaction time is within the claimed range.

Regarding claim 39, Melamede teaches that a decrease in the signal intensity of the first nucleotide in the post-reaction mixture compared to the expected value (i.e. the pre-reaction value) identifies the extension product (column 12, line 58 – column 13, line 3). In determining the expected signal, Melamede inherently performed a pre-reaction analysis of the first nucleotide.

Regarding claim 41, Melamede teaches that the method is performed multiple times for the target position using dATP and dGTP as the added nucleotides (see for example, column 10, lines 1-5).

Regarding claim 42, Melamede teaches that either strand of a double-stranded nucleic acid molecule may be sequenced (see, for example, column 8, lines 46-48).

Regarding claims 47 and 48, Melamede teaches that the detection is by monitoring a differential concentration of a purine or pyrimidine base before and after the synthesizing of the double-stranded molecule (column 12, line 58 – column 13, line 3).

Melamede teaches detection using fluorescence or absorbance spectroscopy, radioactive labeling and counting, or electrochemical detection (column 10, lines 18-24), but does not teach detection using SERS. Melamede also does not teach removal of the sugar moiety from the nucleotides in the post-reaction mixture prior to detection.

Vo-Dinh teaches a method of DNA sequencing using SERS (see abstract). Regarding claim 31, in the method of Vo-Dinh, SERS labeled nucleic acid fragments are cleaved from a target nucleic acid sequence and detected using SERS (column 6, lines 45-52, for example). Vo-Dinh expressly teaches that fluorescence-based sequencing methods may be misleading since they rely upon signals from labels that display broad, structureless and overlapping spectra (column 2, line 67 – column 3, line 9).

Vo-Dinh does not teaching removal of the sugar-phosphate group from the nucleotides prior to deposition on a SERS substrate.

Otto measured surfaced enhanced raman (SERS) spectra for adenine, 2'-deoxyadenosine, dAMP, poly(rA), and denatured DNA (see abstract). Regarding claims 24 and 34, Otto teaches

that the although the SERS spectra for the free nucleotide bases (adenine, guanine, thymine, cytosine, and uracil) are very intense, similarly intense signals were not observed with denatured DNA molecules (see page 1240). Otto then determined that reproducible SERS spectra also could not be obtained for the free nucleotides (dGMP, dUMP, dTMP, dCMP) with the exception of dAMP (page 1240, col. 2). Otto concluded that this inability to obtain reproducible SERS spectra was the result of interference from the sugar-phosphate moiety and stated, "These observations led us to believe that only in the case of dAMP the adsorption is not hampered by the sugar-phosphate group. That is, the presence of the sugar-phosphate group at the N1-position of cytosine, thymine, or uracil and at the N9-position of guanine prevents the adsorption of these nucleotides to the silver surface (page 1240, column 2 – page 1241, column 1)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute Raman detection, specifically SERS detection, for the fluorescence detection taught by Melamede. Vo-Dinh expressly taught that SERS detection was preferable to fluorescence detection in DNA sequencing applications, because fluorescence-based methods inherently suffered from inaccuracies due to the fact that many commonly used fluorescent dyes display broad, structureless, and overlapping spectra (see above). An ordinary practitioner would have been motivated by these teachings of Vo-Dinh to substitute SERS detection for the fluorescence detection taught by Melamede in order to improve the accuracy and sensitivity of the method. An ordinary practitioner would also have been motivated to separate the sugar-phosphate moiety from the nucleotides prior to deposition on the SERS substrate, since Otto taught that the presence of the sugar-phosphate group prevented adsorption of dTMP, dUMP, dCMP, and dGMP to a SERS substrate (pages 1240-1241). Since enzymes capable of removing

the sugar-phosphate group were known in the art and commercially available at the time of invention, an ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Otto to the sequencing method. Finally, regarding the relative concentrations of the dNTP (claims 25 and 26), Melamede expressly taught using an excess (4 equivalents) of the first dNTP in the reaction (column 12, line 58 – column 13, line 3). Although the claimed limitations of: (a) equal amounts of target and dNTP or (b) a dNTP concentration twice as large as the target concentration were not explicitly taught in the above references (Melamede, Vo-Dinh, Otto), an ordinary practitioner would have recognized that the target and NTP concentrations were not critical provided that the functional limitations (ability to reliably detect separated and/or newly incorporated nucleotides) were satisfied and would have optimized target and nucleotide concentrations as necessary in order to achieve the best results. As noted In re Aller, 105 USPQ 233 at 235:

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not inventive and no evidence has been provided to suggest that the use of the particular target and NTP concentrations was anything other than routine or that the results were unexpected as compared to the closest prior art. Therefore, the combined teachings of Melamede, Vo-Dinh, and Otto result in the method of the instant claims 24-27, 30-37, 39, 41-44, 47, and 48.

9. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Melamede (US 4,863,849; cited previously) in view of Vo-Dinh (US 5,306,403; cited previously) and further in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Liang et al. (Chemical Physics Letters (1994) 227: 115-120; cited previously).

The combined teachings of Melamede, Vo-Dinh, and Otto result in the method of claim 24, as discussed above.

None of the above references teach detection using SECARS.

Liang reports the experimental observation of SECARS. Liang teaches that surface enhancement (SECARS) produced a Raman signal significantly enhanced relative to CARS with improved signal-to-noise (see abstract)

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize SECARS detection in the method resulting from the combined teachings of Melamede, Vo-Dinh and Otto. Since Liang taught that the CARS method, which results from excitation with dual lasers, produced a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique, as suggested by Liang, in order to improve the sensitivity of the SERS detection method taught by Vo-Dinh. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS for SERS. Therefore, the ordinary practitioner of the SERS detection method resulting from the combined teachings of Melamede, Vo-Dinh, and Otto, interested in

obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

10. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Melamede (US 4,863,849; cited previously) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US 5,306,403; cited previously) and further in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Quake (US 6,002,471; cited previously).

The combined teachings of Melamede, Vo-Dinh, and Otto result in the method of claim 34, as discussed above.

None of the above references teaches a reaction chamber with at least one dimension less than 100 nm.

Quake teaches a high resolution scanning Raman microscope capable of nanometer level sequencing of DNA based on Raman signals (see abstract and column 2, lines 63-65).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a nanoscale detection device as taught by Quake in the method resulting from the combined teachings of Melamede, Vo-Dinh, and Otto in order to decrease sample requirements and improve the resolution of the method. Quake taught that SERS resolution was increased and sample requirements decreased relative to the prior art of Kneipp, for example (see column 1, lines 38-59 and column 2, lines 6-21). Since the device taught by Quake was specifically designed for Raman-based DNA sequencing applications, the ordinary user would have been motivated to apply the teachings of Quake, thereby resulting in a reaction chamber

having a reduced size (less than 100 nm in at least one dimension, for example), thus resulting in the instantly claimed method.

11. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1; cited previously) in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Sakai et al. (Science (1988) 239: 487-; newly cited).

The combined teachings of Kneipp and Otto result in the method of claim 1, as discussed above.

Regarding claim 49, Kneipp does not teach that the method of claim 1 further comprising synthesizing a double-stranded nucleic acid comprising a nucleotide prior to the separation step.

Sakai teaches a primer-directed method of nucleic acid amplification, specifically PCR (see abstract). This method produces a double-stranded nucleic acid comprising a nucleotide (page 487). Sakai teaches that PCR amplification "is capable of producing a selective enrichment of a specific DNA sequence by a factor of 10^6, greatly facilitating a variety of subsequent analytical manipulations (page 487, column 1)." Sakai further teaches that sequencing is among the subsequent analytical manipulations (page 487, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to obtain a double-stranded nucleic acid comprising a nucleotide via PCR amplification prior to conducting the sequencing method resulting from the combined teachings of Kneipp and Otto. As discussed above, Sakai taught that PCR was a useful method of greatly increasing the amount of a target nucleic acid available for downstream reactions, such as

sequencing (page 487). An ordinary practitioner of the sequencing method resulting from the combined teachings of Kneipp and Otto would have been motivated by these teachings of Sakai to amplify the target nucleic acid prior to detection in order to increase the amount of the target available for the sequencing method. Therefore, the method of claim 49 is prima facie obvious in view of the combined teachings of Kneipp, Otto, and Sakai.

12. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1; cited previously) in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited) and further in view of Sakai et al. (Science (1988) 239: 487-; newly cited) and further in view of Liang et al. (Chemical Physics Letters (1994) 227: 115-120; cited previously).

The combined teachings of Kneipp, Sakai, and Otto result in the method of claim 49.

Kneipp teaches SERS detection rather than SECARS.

Liang reports the experimental observation of SECARS (abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute SECARS detection for SERS detection in the method resulting from the combined teachings of Kneipp, Sakai, and Otto. Liang taught that surface enhancement (SECARS) produced a Raman signal significantly enhanced relative to CARS with improved signal-to-noise (abstract). Since the CARS method, which results from excitation with dual lasers, was known to produce a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique as suggested by Liang in order to improve the

sensitivity of the detection method of Kneipp. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS detection for SERS detection in the method of Kneipp. Therefore, the ordinary practitioner of the SERS sequencing method resulting from the combined teachings of Kneipp, Sakai, and Otto, interested in obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

Statutory Double Patenting under 35 U.S.C. 101

13. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-15 of copending Application No. 11/020,776. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Obviousness-type Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 16-37, 39, and 41-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-44 of copending Application No. 11/020,776 in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited).

Claims 16-44 of the '776 application are recite methods of SERS-based sequencing highly similar to the instant claims 16-37, 39, and 41-44. The primary difference between the instant claims and those of the '776 application is that the instant claims require removal of the sugar moiety from the nucleotide prior to deposition on the SERS substrate.

As discussed in greater detail above, Otto teaches that the sugar-phosphate group prevents adsorption of all nucleotides except dAMP on a SERS substrate. An ordinary practitioner of the method recited by the claims of the '776 application would have been motivated by these teachings of Otto to further include a step of removing the sugar-phosphate

moiety in order to increase adsorption of nucleotide bases on the SERS substrate. Therefore, the instant claims are an obvious variant of the claims recited in copending application 11/020,776.

This is a provisional obviousness-type double patenting rejection.

16. Claims 1-3, 5, and 13-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 8, 11, 12, 17, and 21 of copending Application No. 10/660,902 in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited).

Claims 7, 8, 11, 12, 17, and 21 of the '902 application recite a method of SERS-based nucleic acid sequencing highly similar to the instant claims 1-3, 5, and 13-15. Claims 7, 8, and 17 of the '902 application recite a method that is a more specific embodiment of the method recited in the instant claims 1-3 and 5 with the exception that the '902 application does not teach separation of the sugar-phosphate group from the nucleotides. The limitations recited in the instant claims 13-15 are recited in claims 11, 12 and 21 of the '902 application.

As discussed in greater detail above, Otto teaches that the sugar-phosphate group prevents adsorption of all nucleotides except dAMP on a SERS substrate. An ordinary practitioner of the method recited by the claims of the '902 application would have been motivated by these teachings of Otto to further include a step of removing the sugar-phosphate moiety in order to increase adsorption of nucleotide bases on the SERS substrate. Therefore, the instant claims are an obvious variant of the claims recited in copending application 10/660,902.

This is a provisional obviousness-type double patenting rejection.

17. Claims 1, 2, 4-7, 9, 10, and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-10, 12, 15, 17, 18, and 21-23 of copending Application No. 11/270,211.

Claims 1, 3, 6-10, 12, 15, 17, 18, and 21-23 of the '211 application recite a method of SERS-based nucleic acid sequencing highly similar to the instant claims 1, 2, 4-7, 9, 10, and 12. Claims 1, 9, 12, and 15 and also claims 17 and 23 of the '211 application recite a method that is a more specific embodiment of the method recited in the instant claim 1 and therefore anticipate this claim. The limitations of the instant claim 2 are recited in claims 3 and 21 of the '211 application. The limitations of the instant claims 4-7, 9, 10, and 12 are recited in claims 6-8, 10, 18, and 22 of the '211 application.

This is a provisional obviousness-type double patenting rejection.

18. Claims 1-4 and 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, and 7 of US 6,972,173 B2 in view of Otto et al. (Journal of Physical Chemistry (1988) 92: 1239-1244; newly cited).

Claims 1, 3, and 7 of the '173 patent recite a method of SERS-based nucleic acid sequencing highly similar to the instant claims 1-4 and 9. Claims 1, 3, and 7 recite a method that is a more specific embodiment of the method recited in the instant claims 1-4 and 9 with the exception that the '173 patent does not teach separation of the sugar-phosphate group from the nucleotides.

As discussed in greater detail above, Otto teaches that the sugar-phosphate group prevents adsorption of all nucleotides except dAMP on a SERS substrate. An ordinary

practitioner of the method recited by the claims of the '173 patent would have been motivated by these teachings of Otto to further include a step of removing the sugar-phosphate moiety in order to increase adsorption of nucleotide bases on the SERS substrate. Therefore, the instant claims are an obvious variant of the claims recited in the '173 patent.

Response to Arguments

19. Applicant's arguments, see page 8, filed January 12, 2007, with respect to the rejection of claims 1-15, 18-22, and 45 under § 112, 1st paragraph (enablement and new matter) have been fully considered and are persuasive. Applicant's amendment to the claims overcomes the rejection, and therefore, it has been withdrawn.

Applicant's arguments with respect to claims 16, 17, 24-44, and 46-48 have been considered but are moot in view of the new ground(s) of rejection.

Regarding the outstanding provisional obviousness-type double patenting rejections, Applicant submits that no action is required at present, since the rejections are provisional (page 9). MPEP 804 states, "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications." Since the provisional double patenting rejections are not the only rejections remaining in the instant application, they are maintained.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
March 31, 2007

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